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JOURNAL CLUB

Article Summary by: Michael Strong, PhD

ARTICLE

Article Title: Mycobacteriophage–antibiotic therapy promotes enhanced clearance of drug-resistant Mycobacterium abscessus. Matt D. Johansen, Matthéo Alcaraz, Rebekah M. Dedrick, Françoise Roquet-Banères, Claire Hamela, Graham F. Hatfull, Laurent Kremer. *Disease Models and Mechanisms*, (2021) 14 (9): dmm049159.

CLINICAL QUESTION

Can mycobacteriophage be used in conjunction with antibiotics to provide more effective means to lyse, kill, and clear severe nontuberculous mycobacterial (NTM) infections, including *Mycobacterium abscessus* infections? And, how can these phage and antibiotic combinations be efficiently screened *in vivo* using a zebrafish experimental model system?

SUMMARY

With the increasing numbers of nontuberculous mycobacterial (NTM) pulmonary infections, particularly in individuals with cystic fibrosis (CF), combined with the difficult nature of treatment of patients with NTM infections, it has become clear that innovative developments of new ways to combat NTM infections are greatly needed. Among the ideas of current focus, bacteriophage therapy that targets specific NTM species and strains has recently shown promise in limited compassionate use clinical cases. As such, there needs to be additional experimental focus on the elucidation of the mechanisms of mycobacteriophage action *in vivo*, leveraging model systems, including the study of phage in combination with antibiotics.

In this research article, Johansen and colleagues examine the *in vitro* and *in vivo* activity of the mycobacteriophage named Muddy, against *M. abscessus* clinical and reference strains. The researchers demonstrate that Muddy effectively lyses the clinical *M. abscessus* subspecies *massiliense* strain GD01 *in vitro*, and that this lysis is significantly enhanced in combination with certain drugs. The researchers also examined the *in vivo* activity of Muddy using a zebrafish model system, including a cystic fibrosis transmembrane receptor CFTR-depleted zebrafish model. Mycobacteriophage plus antibiotics resulted in a significant increase of zebrafish larval survival and a decrease in pathological signatures. Interestingly, the phage activity was significantly reduced *in vivo* in when macrophage were not functional, suggesting that macrophage and a functional innate immune system may be important for effective mycobacteriophage therapy.

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GROUP OPINION

The zebrafish and CFTR-depleted zebrafish model provides a fast, efficient, and effective model system for screening *in vivo* activity of mycobacteriophage and mycobacteriophage-drug combinations. Based on the results of this paper, and results of clinical compassionate use cases of mycobacteriophage, the field of phage therapy for NTM treatment is likely to provide additional tools in the arsenal to treat NTM infections effectively, and mycobacteriophage therapy is an area in need of additional and mechanistic research insights, some of which can be addressed using *in vivo* model systems.

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